REMARKS

Claim Amendments

Claims 1, 4 and 5 have been amended so that all contain parallel language.

Recently cancelled claims 6 and 7 have been added back as new claims 16 - 18, directed to a method of identifying the minimum portion of a lysyl oxidase pro-peptide, and, in particular, the lysyl oxidase pro-peptides having the amino acid sequence of SEQ ID NO.: 1 or SEQ ID NO.: 2.

Applicants submit that no new matter has been added by these amendments.

Applicants further submit that Applicants' amendment or cancellation of certain rejected claims is not to be construed as an admission that the Examiner's rejections were proper. The Applicants continue to believe that the rejected claims are described in and enabled by the specification, and are not obvious in view of the cited references, as argued herein and as previously argued. The rejected claims have been amended or cancelled for the sole purpose of advancing the case to allowance. The Applicants reserve their rights to file continuing applications to continue the prosecution of the rejected claims.

Rejections Under 37 C.F.R. § 112

The pending claims have been rejected as not satisfying the written description requirement and for lack of enablement. This rejection, again, is respectfully traversed in light of the arguments herein.

The Examiner's argument as to both requirements, given in pp. 2-5 of the Advisory Action, seems not to be taking into account

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that in the previous paper, Applicants amended the claims to recite that "said lysyl oxidase pro-peptide portion of said polypeptide is that of human, mouse or rat." The Examiner's assertions such as that the claims are directed to "any" lysyl oxidase pro-peptide having "any structure" and that one of skill in the art would have difficulty envisioning the "structure of additional lysyl oxidases" seems not to address the actual language of the pending claims.

The Examiner is respectfully requested to review the previous rejections for lack of both written description and enablement.

Rejections Under 37 C.F.R. § 102 (b)

Claims 1-3 continue to be rejected as anticipated by Li et al. (WO/0185157) ("Li"), the Examiner saying that this reference teaches "a therapeutic composition comprising a lysyl oxidase polypeptide without catalytic activity for the treatment of cancer/tumors." The Examiner cites to p. 10, lines 25-33 and p. 13, lines 25-28 of Li.

Applicants submit, as they have stated before, that the statements of Li cited by the Examiner ***are directly contradicted*** by ***all other statements in the Li application that relate to concrete results***, including the experiments described in the Examples. Thus, the statements of Li cited by the Examiner were ***merely gratuitous on the part of the authors, contradicting the authors' own experimental evidence.***

Consequently, the specific statements of Li that were cited by the Examiner would not have been accepted as believable by those of ordinary skill in the art at the time of the filing of the instant application, given all of the evidence to the contrary

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in the document. The Examiner in the Final Office Action continued to rely on the cited statements at pp. 10 and 13 of Li and did not provide an answer to the Applicants' arguments, which are presented again below.

In particular, in relation to Applicants' invention, ***all examples provided by Li present results that depend directly on lysyl oxidase catalytic activity for their effects, in sharp contrast to the instant claims that unambiguously exclude lysyl oxidase catalytic activity.***

Therefore, Li cannot anticipate Applicants' claims 1-3. For example, starting in the Brief Summary of the Invention, at p. 4, lines 3-5, the Li specification states: "Administered in a pharmaceutically acceptable inert carrier substance, the inhibitor ***oxidizes*** cell growth factors ***at lysine residues.***" This same mechanism of action is further recited in the summary at p. 4, lines 16-18; p. 4, lines 25-29; and p. 6, lines 14-20. All of these cites are describing the ***normal catalytic activity of lysyl oxidase (LO)***, which is to ***oxidize specific lysine residues***, as pointed out in Li at p. 11, lines 3-5.

The rest of the paragraph on p. 11 that starts at line 3 describes a number of specific proteins that the prior art had recognized as being substrates for LO. ***All that is contributed by Li*** is a recognition that ***additional substrates of LO exist*** and that by acting on these additional substrates using the ***normal catalytic activity of LO***, i.e., ***oxidizing*** these additional substrates ***at specific lysine residues***, a new effect can be obtained. This point is spelled out in Li in summary form at p. 15, lines 8-25, and is supported by experimental results cited at least at p. 43, lines 15-27; p. 50, lines 18-31; p. 52, lines 3-8;

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p. 53, lines 9-15; and 55, lines 6-14. This point is further supported in Li by the conclusion given at p. 57, line 18 - p. 58, line 20, that it is the ***catalytic activity of LO*** that is responsible for this ***therapeutic*** effect.

In all of this discussion, Li uses the terminology "LO," meaning "lysyl oxidase." Li does ***not*** mean the proenzyme form of lysyl oxidase. In fact the proenzyme is discussed only once - in the paragraph starting at p. 12, line 28 - in a discussion of the synthesis of LO, where it is stated:

> ***LO*** is synthesized by fibrogenic cells as a ***46 kDa [kDa] proenzyme.*** Following signal peptide cleavage and N-glycosylation the resulting 50 kDa [kDa] proenzyme is secreted and then proteolytically cleaved to the ***31 ± 1 kD functional species*** in the extracellular space[, releasing the pro-peptide].
>
> (emphasis and additional wording added)

Although Li does at p. 13 use the terminology "fragments and/or derivatives of LO and/or its homologues, with or without catalytic activity" to describe the claimed inhibitors as pointed out by the Examiner, on the very next page of the specification (p. 14) there is a more believable statement about what ***Li means to teach***:

> The therapeutically effective portion refers to a compound or composition effective to depress, suppress or inhibit mitogenesis, angiogenesis, or the transactivation effects of Tat. Such therapeutic agents include purified naturally occuring LO, human recombinant LO and ***catalytically active*** fragments (peptides) of LO.
>
> (Li et al., p. 14, lines 1-6, emphasis added)

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Finally, the Applicants' position as to the true teaching of Li is further reinforced by the language of independent claims 1-3 of Li as published, in that the second "wherein" statement of each of claims 1-3 reads "wherein said inhibitor ***oxidizes*** said [growth factor / angiogenic factor / transactivator] ***at lysine residues***," emphasis added. In other words, Li claims ***only*** "inhibitors" ***having the catalytic activity of LO***.

As Li thus teaches that a ***catalytically active LO*** (or portion thereof) is required for the disclosed ***therapeutic activity***, the reference is ***necessarily*** teaching a "functional" species as that term is defined on p. 12, starting at line 28, i.e., species that ***does not contain the pro-peptide portion of the LO proenzyme***. Yhis requirement in Li is in direct contrast to the requirements of the ***Applicants' claims*** in the instant application.

Therefore, Applicants submit that Li cannot anticipate Applicants' claimed invention, where the therapeutically active polypeptide in the claimed therapeutic composition ***is*** a portion of a lysyl oxidase pro-peptide and wherein the claimed polypeptide ***does not*** have lysyl oxidase catalytic activity. Thus, the rejection is overcome.

Nor would Li, whether or not it is combined with other references, make obvious the Applicants' instant claims. As summarized above, Li teaches that a therapeutically active polypeptide ***must*** have the catalytic activity of lysyl oxidase, whereas Applicants teach and claim a therapeutic composition ***having a different therapeutically active polypeptide***, i.e., one with ***the directly opposite activity***. Thus, Li could never lead one of ordinary skill to, and thereby make obvious, the

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Applicants' claimed therapeutic composition, which must ***not*** have lysyl oxidase catalytic activity.

The Examiner is respectfully requested to review this argument again pertaining to the LI reference and to point out to the Applicants' undersigned attorney where the Examiner believes the Applicants' reasoning is unsound.

Applicants submit that all claims are in condition for allowance and such action is respectfully requested.

The Examiner is encouraged to telephone the undersigned attorney to discuss any matter that would expedite allowance of the present application.

Respectfully submitted,

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